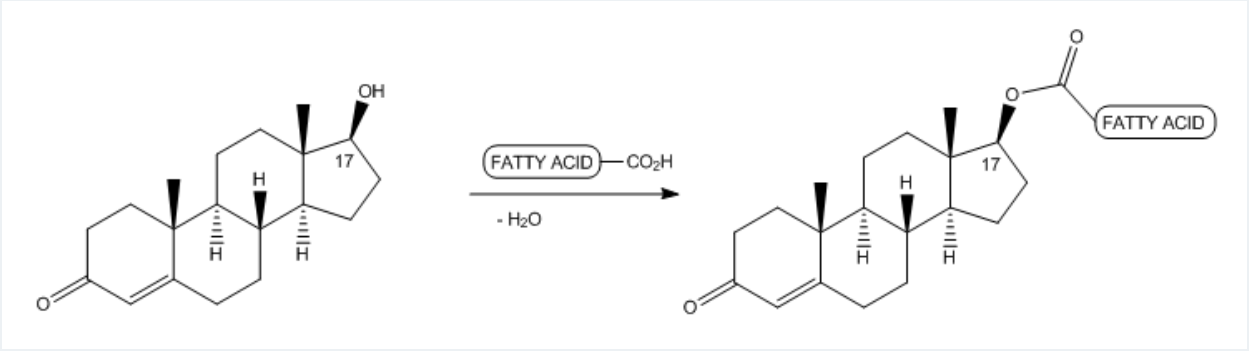
Pharmacology 101

Pharmacology is the area of science concerned with drugs and their exerted effect on biological systems. Pharmacokinetics, a sub-branch of pharmacology, is the study of the processes of absorption, distribution, metabolism and elimination of drugs within the body. Collectively, these four components are termed disposition. Steroids can display differing pharmacokinetic characteristics depending on their structure, which in turn determines their behavior (and therefore concentration) in the blood. It therefore stands to reason that in order to design an effective steroid cycle, one must have a sound understanding of steroid pharmacokinetics.

In this discussion, we will focus on the area of absorption, since this has the greatest impact on steroid cycle design. Furthermore, since cycle design is predominantly influenced by the injectable components of a cycle, the bulk of this discussion will be concerned with intramuscular routes of steroid administration.

Testosterone esters are the most commonly used form of injectable steroid. Both oral and intramuscular administration of free testosterone is relatively ineffective due to rapid elimination from the body via complete metabolism by the liver; both large and regular doses would therefore be required to be therapeutically useful. In order to make testosterone more user–friendy, it is formulated into a controlled release (depot) preparation by chemical modification (esterification) of the C–17 hydroxyl group with a variety of fatty acid chemical subunits. Testosterone esters are therefore considered to be "prodrugs" because they are metabolized to active steroid when the ester is hydrolyzed upon entering the general circulation. See structures.



Controlled release preparations are designed to provide a slow and sustained rate of absorption in order to minimise fluctuations in the plasma concentration versus time profile during the interval between doses. The activity of the steroid is therefore prolonged, and the injection frequency reduced. The rate of release from the injection depot into the extracellular fluid is primarily governed by the oil/water partition coefficient (termed "logP") of the steroid ester. Put simply, this means that since the steroid has to make its way into the hydrophilic (“water loving”) environment of the blood in order to be metabolized to active steroid, its tendency to do so decreases as the fatty acid attached to testosterone becomes longer due to the greater hydrophobicity (“water fearing”) of the steroid ester. A simple analogy is to think about the process of trying to mix oil and water. Once absorped from the intramuscular depot, the testosterone ester is rapidly hydrolysed in plasma to the unesterified active metabolite. The table below gives logP values for several commonly used injectable steroid esters. Notice how the logP value increases (ie. steroid hydrophobicity increases) as the number of carbon atoms on the fatty acid side chain increases.

Partition coefficients of some common steroids

Name	logP	# carbons

		(side-chain)
nandrolone (parent)	2.54	—
testosterone (parent)	3.31	—
testosterone propionate	3.90	3
stanozolol	4.37	—
testosterone isocaproate	5.06	6
testosterone enanthate	5.57	7
testosterone cypionate	5.40	8
nandrolone phenylpropionate	5.03	9
testosterone phenylpropionate	5.50	9
nandrolone decanoate	6.35	10
testosterone decanoate	6.82	10
boldenone undecylenate	6.95	11
testosterone undecanoate	7.24	11

The table below outlines the half–life ($t_{1/2}$) of some commonly used injectable steroids, as determined from several scientific studies involving human subjects. What is a half–life? The ($t_{1/2}$) of a steroid is the time taken for the concentration or amount of steroid in the body to be reduced by 50%. For example, if the initial concentration of a steroid was 50 units, then after one half–life, the concentration would be 25 units; after two half–lives, the concentration would be 12.5 units, and so on. Strictly speaking, we refer to a steroid's half–life as its disposition half–life. Notice how differences in both injection volume and injection site can alter a given steroid's ($t_{1/2}$). This observed variability can be attributed to the differences in tissue composition and blood flow between different injection sites, the location from which the steroid must diffuse between loose connective tissue and muscle fibers to reach the general circulation. Genetic variability between subjects (eg. race, sex) will also have an effect on steroid pharmacokinetics. Therefore, steroid half–lives derived from the scientific literature should be taken only as a rough estimate. What is important to note is that the data trends in the direction we would expect on the basis of hydrophobicity: as the logP increases, so does the half–life. Knowing this trend, one can reasonably interpolate the half–life of any oil-based steroid given its logP value (boldenone appears anomalous in this regard, but the study was performed in horses, so we can't make a direct comparison with human data). For more information on steroid half–lives, refer to the resource library.

Half-Lives of Injectable Steroids in an Oil Vehicle

Name	logP	# carbons (side-chain)	Volume (mL)	Amount (mg)	Location	Half-life (days)	Ref
testosterone propionate	3.90	3	1	25	--	1	1
stanozolol[a,b]	4.37	--	--	--	--	3.4	2
testosterone enanthate	5.57	7	--	--	--	4.5	3
nandrolone phenylpropionate	5.03	9	4	100	gluteal	2.4	4
nandrolone decanoate	6.35	10	4	100	gluteal	7	4
nandrolone decanoate	6.35	10	1	100	gluteal	7.7	4
nandrolone decanoate	6.35	10	1	100	deltoid	12	4
nandrolone decanoate	6.35	10	1	50	gluteal	7.1	5
nandrolone decanoate	6.35	10	1	100	gluteal	11.7	5
nandrolone decanoate	6.35	10	1	150	gluteal	11.8	5
boldenone undecylenate[a]	6.95	11	--	--	--	5.1	2
testosterone undecanoate	7.24	11	2	500	--	18.3	6
testosterone undecanoate	7.24	11	4	1000	--	23.7	6

[1] *J CLIN ENDOCR METAB.*, **1986**, *63*, 1361-1364

[2] *J VET PHARMACOL THERAP.*, **2007**, *30*, 101-108

[3] *TESTOSTERONE-ACTION, DEFICIENCY, SUBSTITUTION, 3rd Ed. New York: Cambridge University Press* **2004**, Ch.14

[4] *J PHARMACOL EXP THER.*, **1997**, *281*, 93-102

[5] *J CLIN ENDOCR METAB.*, **2005**, *90*, 2624-2630

[6] *J ANDROL.*, **1998**, *19*, 761-768

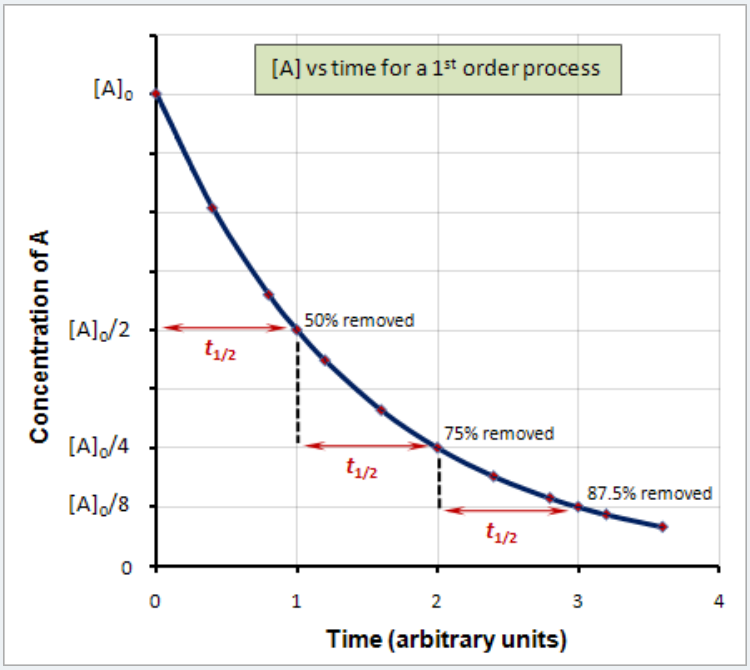
[a] In horses

[b] aqueous suspension vehicle

From a kinetic viewpoint, the rate of appearance of steroid in the blood following an intramuscular depot injection is governed by several simultaneous processes. If one were to measure the levels of steroid in the blood as a function of time, what is typically observed is a rapid increase in concentration (characterized by an initial steep ascending phase of the concentration versus time curve) followed by a relatively slow decrease in concentration (characterized by a relatively shallow descending phase of the concentration versus time curve). The former process reflects the combined processes of hydrolysis of the ester and of its subsequent distribution and elimination whereas the latter process represents the process of ester release (absorption) from the injection depot into the bloodstream.

Thus, the overall behavior of a steroid in the blood (its rate of appearance and subsequent disappearance) is dependent upon several simultaneous processes, all of which display differing half–lives, making mathematical deconvolution of each individual process kinetically difficult. However, a characteristic of depot formulations is that the process of steroid release from the injection depot to the general circulation is the slowest process of all, making it the rate–limiting step in the sequential/parallel processes of absorption, distribution and elimination. For this reason, the situation is now simplified because the plasma concentration–time profile tends to closely parallel rate of absorption. Put another way, the half–life of a steroid, when administered as a depot preparation, is a reflection of the rate and extent of absorption and not elimination or distribution. It therefore follows that by simply having some knowledge a steroid's disposition half–life, we can, to a very good approximation, predict how the concentration of steroid in our body changes with time.

The disposition of most drugs follows first–order kinetics. In the context of steroids, a first–order kinetic process is one in which a constant proportion of steroid is eliminated during a finite period of time regardless of the drug amount or concentration. Because a constant fraction of steroid is removed per unit time, the absolute amount of steroid removed is proportional to the concentration of steroid. Thus, when the concentration is high, more steroid will be removed than when it is low. Consequently, the decline in concentration approaches completion asymptotically, and theoretically the steroid concentration should decline indefinitely. For practical purposes, the decline is essentially complete (97%) after five half–lives, resulting in a negligible amount of steroid remaining in the body. The graph below illustrates this concept for a steroid "A".



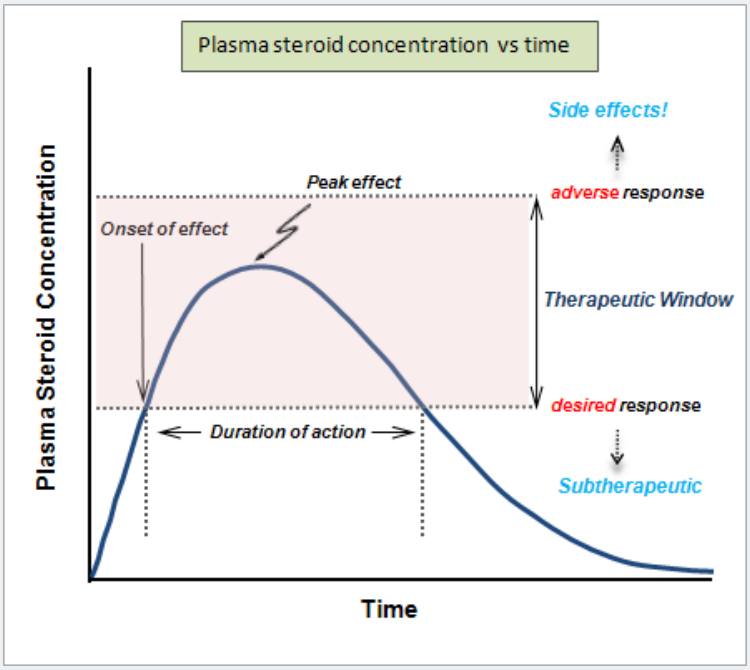
Half-Lives and Percent Steroid Removed

Number of half-lives	% of steroid remaining	% of steroid removed
0	100	0
1	50	50
2	25	75
3	12.5	87.5
4	6.25	93.75

5	3.125	96.875

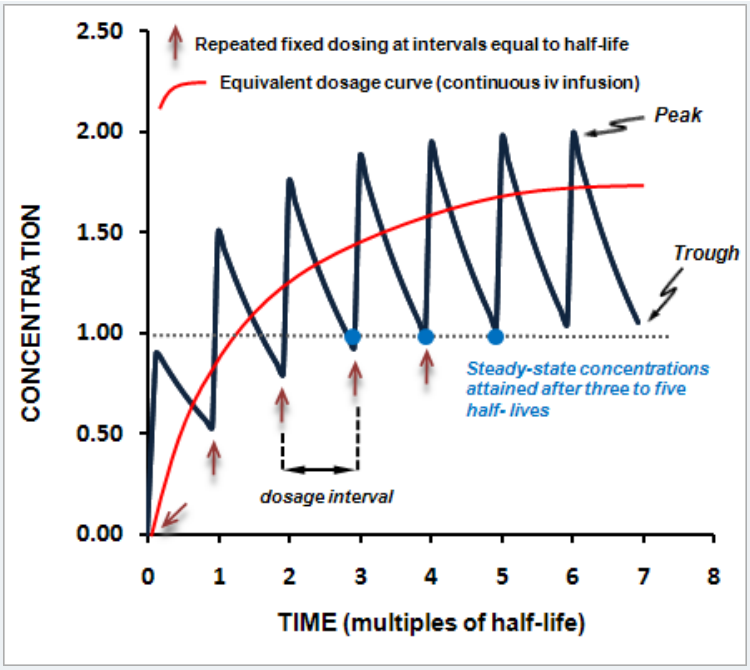
It is therefore quite obvious that the rate of absorption of a steroid can be an important consideration for determining a dosage regimen. By knowing a steroid's disposition half–life, we can make predictions about how the concentration of steroid in our body changes with time by using a first–order kinetic model to calculate concentration versus time relationships. This is the premise of **The Anabolic Steroid Calculator**.

In order to construct an effective dosage regimen, the main factors to consider are: dosage amount, dosage frequency/interval, and pre–loading. Short acting steroids (eg: testosterone propionate, $t_{1/2}$ ~1 day) have relatively short half–lives whereas long acting steroids (eg: nandrolone decanoate, $t_{1/2}$ ~7–12 days) have relatively long half–lives. Since short acting steroids are cleared from the body more rapidly, they need to be given in regular doses to build up and maintain a high enough concentration in the blood to be therapeutically effective. In either case, the goal is to adjust the dosage regimen such that the blood plasma concentration of steroid is maintained within the therapeutic window. The therapeutic window is the safe range between the minimum therapeutic concentration (that delivers the desired pharmacologic effects, ie. building muscle!) and the minimum toxic concentration (that delivers unwanted pharmacologic effects, ie. side effects!) of the steroid in question.



The pink shaded area on the graph of Plasma Steroid Concentration vs Time represents the therapeutic window. If the concentration falls below the desired response level, we say the dosage is 'subtherapeutic'. At this level, we have not dosed a sufficient amount of steroid in order to fully activate/saturate our androgen receptors for maximum muscle building. At the other extreme, excessive dosing can lead to an adverse response, in which unwanted side–effects may be observed. Large swings in steroid plasma level concentrations should therefore be avoided, and ideally the concentration should minimally fluctuate between the upper (peak) and lower (trough) boundaries of the therapeutic window (a 2–fold fluctuation is considered acceptable). This is known as a steady state, and it occurs when the amount of steroid in the plasma has built up to a concentration level that is therapeutically effective and as long as regular doses are administered to balance the amount of steroid being cleared the steroid will continue to be active. This poses an obvious question: what constitutes the optimum therapeutic window for anabolic steroid use? Unfortunately, there is no firm answer for this! For a given steroid, the therapeutic dose for a novice user may differ greatly from that of an advanced user. Furthermore, not all steroids are created equal–some provide greater gains than others, but with the associated cost of increased toxicity (and thus narrower therapeutic window). Age, race and sex will also play a role in how well you respond to anabolic steroids, and your tolerance to side–effects. Sadly, the general consensus is to adjust doses conservatively, and examine the effect.

The time taken to reach the steady state is determined by the $t_{1/2}$ of the steroid in question. If you dose your steroid at intermittent intervals equivalent to its $t_{1/2}$, you will achieve steady state within 3–5 half-lives. In three half–lives, serum concentrations are at approximately 90% of their ultimate steady–state values. For example, if you admininstered a set amount of steroid every 6 days, and its half–life was 6 days, then the plasma levels will reach a steady state within 18–30 days. At this point, the equivalent of one dose is eliminated each dosing interval (half–life).

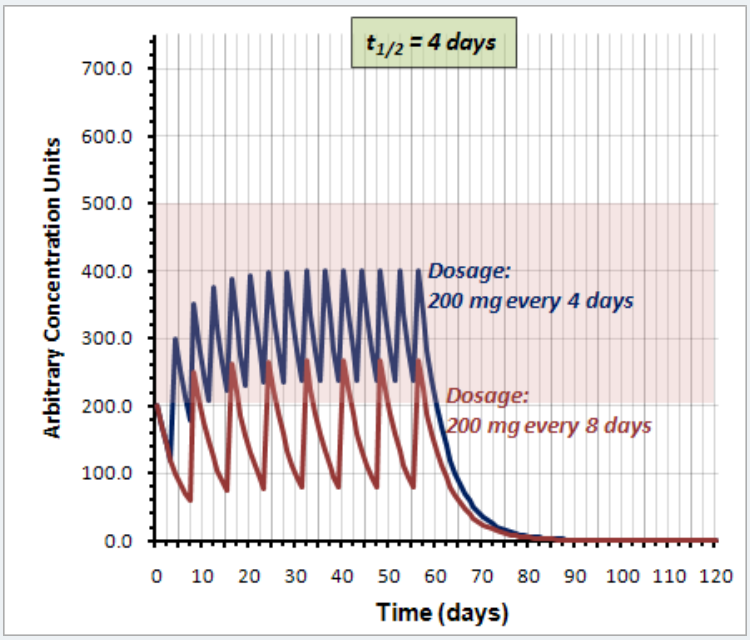


Importantly, at steady–state with a dosing interval equal to the half–life, the plasma concentration fluctuates within a two–fold window over the dosing interval and the amount of steroid in the body shortly after each dose is equivalent to twice the maintenance dose. Furthermore, the steady state plasma concentration averaged over the dosing interval is the same as the steady state plasma concentration for a continuous infusion at the same dose rate (red line on graph above).

So now that we know how a steroid's half–life can influence its behavior in the body, we apply this knowledge to design an effective steroid cycle. As mentioned above, dosing at intervals equivalent to a steroid's half–life will achieve steady–state in 3–5 half–lives. But what effect would dosing at intervals smaller or larger than the half–life have on the overall concentration–time profile? For drugs with a long half–life compared with the dosing interval, the drug will markedly accumulate. For drugs with a short half–life compared with the dosing interval, most of the drug is eliminated between doses, with little accumulation. Therefore it is important to ensure your dosing schedule (interval) is aligned with the half–life of your steroid.

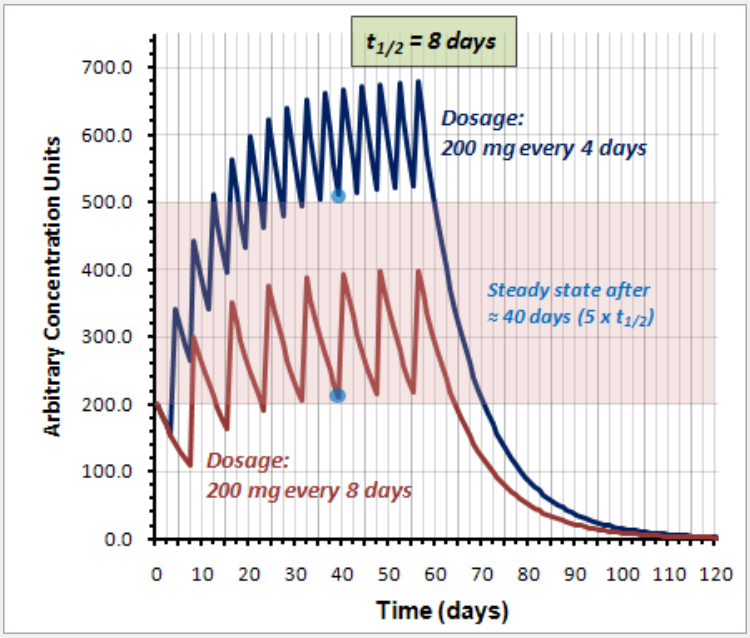
Dosing a fixed amount of steroid at regular intervals (maintenance dose):
Let us consider two steroids differing in their half–life by a factor of two, each with a hypothetical fixed dosing schedule of 200 mg per dosage interval.

- Scenario One ($t_{1/2}$ = 4 days)



A dosing schedule of 200mg every 4 days leads to a steady state in approximately 3 weeks (ie. 5 x $t_{1/2}$). The concentration fluctuates within a 2–fold window, and the maximum concentration does not exceed 400 "units" (ie. 2 x the maintenance dose). If we assume that the ideal therapeutic range falls within the pink shaded area, then this dosing strategy will be therapeutically effective. If we now *double* the dosing interval to 200 mg every 8 days, the concentration now fluctuates within a 3–fold window, the maximum concentration is now less than twice the maintenance dose, and importantly, a significant portion of the concentration-time profile is spent outside of the therapeutic window. This makes sense when you consider that the longer you wait between doses, the greater the clearance of steroid from your body, and thus the concentration never gets high enough to be therapeutically optimal.

- Scenario Two ($t_{1/2}$ = 8 days)



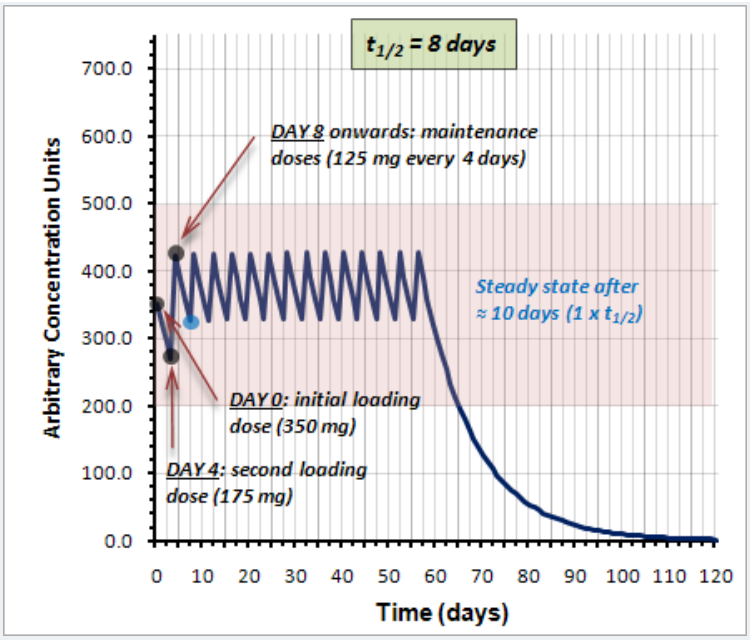
So how does the previous example compare with a steroid possessing a half–life of eight days instead of four? Once again, you can see that a dosing schedule of 200mg every 8 days (ie. dosing at intervals equivalent to steroid half–life) leads to a steady–state in approximately 6 weeks (ie. 5 x $t_{1/2}$), with a 2–fold fluctuation in concentration. If we now *halve* the dosing interval to 200mg every 4 days, there is a significant accumulation of steroid simply because you are not allowing the body enough time to clear the previous dose before the next dose. Time to reach steady–state is relatively unchanged, and the fluctuation window is narrower, but the concentration–time profile may exceed the therapeutic range, leading to undesirable side-effects.

Based on the above observations, the key points for dosing a fixed amount of steroid at regular intervals can be summarized as follows:

- if you dose at intervals equal to the steroid's half–life, you will reach steady–state in approximately five half–lives. Multiplying the half–life by 0.714 will give you the number of weeks to reach steady–state. For example, for $t_{1/2}$ = 8 days, steady–state is reached within 5.7 weeks (8 * 0.714). Similarly, for $t_{1/2}$ = 6 days, steady–state is reached within 4.3 weeks (6 * 0.714);
- if you dose at intervals equal to the steroid's half–life, the concentration will fluctuate within a 2–fold window;
- the amount of steroid in the body shortly after each dose is equivalent to twice the maintenance dose when dosing at intervals equal to $t_{1/2}$;
- the longer the half–life, the longer it takes to reach steady–state.

Loading doses:

For steroids with a relatively short half–life, you can reach a steady–state within a reasonable time frame using a fixed dosing strategy. However, as we saw with the example above, as the steroid's $t_{1/2}$ becomes longer, the induction period to reach steady–state becomes unacceptably long (eg. approximately 6 weeks when $t_{1/2}$ = 8 days). We can reduce the induction period while still adopting a fixed dosing strategy by the use of a loading dose. A loading dose is one dose or a series of doses given at the onset of a cycle with the aim of achieving the target concentration rapidly. Let's look again at the example with $t_{1/2}$ = 8 days.



In this example, two loading doses are given on day zero (350 mg) and day four (175 mg), followed by repetitive doses of 125 mg at four day intervals. The loading dose strategy has a dramatic effect on the induction period, reducing the time to reach steady–state by a factor of four (10 days vs 40 days), and steroid levels oscillate within a tight concentration range within the therapeutic window. For more examples of hypothetical scenarios, refer to the cycle example page.

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